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EXAMINER	
BAKALYAR,H	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

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Office Action Summary	Application No. 08/491,888	Applicant(s) Rigler
	Examiner Heather Bakalyar	Group Art Unit 1645

☒ Responsive to communication(s) filed on *Jun 23, 1998* .

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *3, 11, 17-21, 23-27, and 39-106* is/are pending in the application.

Of the above, claim(s) *3, 11, 17-21, 23-27, 39-84, and 102-106* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *85-101* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. The amendment filed 6/23/98 (Paper No. 20) is acknowledged and has been entered.

Claim(s) 1, 2, 4-10, 12-16, 22, 28-38 have been canceled.
Claim(s) 85-106 have been added.
Claim(s) 3, 11, 17-21, 23-27, 39-106 are pending and subject to restriction/election requirement.

Election/Restriction

3. Applicants second traversal of the restriction requirement substantively identical to that of Paper No(s). 12 is noted, but is not persuasive for the reasons previously set forth.

4. Newly submitted claims 102-106 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the claims read on previously non-elected species II (3, 4) as per page 5 of Paper No(s). 10 filed 4/15/97.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 102-106 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

5. Claims 85-101 are examined. Claims 3, 11, 17-21, 23-27, 39-84, 102-106 are withdrawn from consideration as being drawn to a non-elected invention.

Claim Objections

6. Claim 90 is objected to because of the following informalities: "trnaslational" on line 3 should be spelled --translational--. Appropriate correction is required.

Claim Rejections - 35 U.S.C. § 112

7. Claims 85-101 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation(s) of "assaying" in claim(s) 85 is/are vague and indefinite because it is not known what characteristic or property of the molecule(s) is being measured (e.g. number in a sample, chemical properties etc). It is noted that no method steps clarify this issue.

Claim 85 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: it is not recited to what the determined material parameters are being correlated. This omission further renders the goal and process of the claimed invention sufficiently vague that one of skill in the art would not be reasonablely apprised of what is encompassed by the claims because (a) the preamble does not define what is assayed and (b) no method steps which define how determined values are correlated are recited. Also see "Response to Arguments", below.

Claim Rejections - 35 U.S.C. § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claim Rejections - 35 U.S.C. § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 85-93 are rejected under 35 U.S.C. 102(b) as being anticipated by Thompson et al Biophys. J. July 1983 volume 43 pages 103-114, or; Sorscher et al Biochimica et Biophysica Acta 610(1980) pages 28-46; Kask et al Eur Biophys J (1985) 12: 163-166, or; Rigler et al Fluorescence Spectroscopy (Wolfbeis, editor) Springer Verlag (1992) pages 13-24, or; Meyer et al, Biophys. J. (1988) volume 54 pages 983-993.

Thompson et al, or Sorscher et al, or Kask et al or, Rigler et al or, Meyer et al, each teach methods for identifying (detecting) molecules in dilute solutions (dilute, therefore reads on a small

number of molecules) using laser-excited FCS with measuring times of less than 500 ms (e.g. channel time 0.1 ms) in a small volume element (e.g. 10^{-15} liter and below) and short diffusion times by determining the molecules' material-specific parameters (e.g. rotational motion, rotational diffusion, translational diffusion, chemical kinetics, excitation/emission wavelengths, or lifetime of the excited state), which parameters are in turn determined by luminescence measurements (using detecting optics) of the molecules. Rigler et al, for example, disclose that it is standard in FCS methodology to correlate translational diffusion (G(t)) with the absolute number of particles (N) and exemplify this technique with a receptor bound to a rhodamine-labeled inhibitor (reads on ligand or ligand complex, complex of ionic, e.g. receptor-ligand/inhibitor, and non-ionic nature, e.g. label-inhibitor, and ternary complex). The general technique of FCS comprises taking fluorescent measurements in an electric or magnetic field (e.g page 104, "Theory", line 3 of Thompson), further it is noted that due to Earth's natural magnetic field, a magnetic field is superimposed upon every Earthly object, including objects associated with FCS measurements. Multiple means of varying space coordinates of the measuring volume are disclosed, for example Sorscher on Figure 1 teaches that sample and the focal point of the laser beam can be displaced with respect to each other; mirrors which read on detecting optics are adjusted as in Meyer, Figure 2).

11. Claims 96-101 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thompson et al Biophys. J. July 1983 volume 43 pages 103-114, or; Sorscher et al Biochimica et Biophysica Acta 610(1980) pages 28-46; Kask et al Eur Biophys J (1985) 12: 163-166, or; Rigler et al

Fluorescence Spectroscopy (Wolfbeis, editor) Springer Verlag (1992) pages 13-24, or; Meyer et al, Biophys. J. (1988) volume 54 pages 983-993; in view of facts well known in the art.

Thompson et al Biophys. J. July 1983 volume 43 pages 103-114, or; Sorscher et al Biochimica et Biophysica Acta 610(1980) pages 28-46; Kask et al Eur Biophys J (1985) 12: 163-166, or; Rigler et al Fluorescence Spectroscopy (Wolfbeis, editor) Springer Verlag (1992) pages 13-24, or; Meyer et al, Biophys. J. (1988) volume 54 pages 983-993, are discussed, supra.

It may be determined that the labels of the prior art references are not "luminophorous", or in particular that the labels of the prior art references do not have the particular extinction coefficient or quantum yield recited in instant claim 98. It may also be determined that configuration of measuring compartments and emergence objective are not as per instant claim 99.

If it is determined that, for example, a rhodamine label does not read on a luminophorous label, such luminophorous labels were well known in the art at the time of invention and were recognized functional equivalents with rhodamine labels, especially in FCS methodology. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute luminophorous labels for the labels of Thompson et al, or; Sorscher et al or; Kask et al, or; Rigler et al or; Meyer et al, because luminophorous labels were well known in the art at the time of invention and were recognized functional equivalents with rhodamine labels, and one of ordinary skill in the art would have been motivated to substitute with the expectation of successfully performing FCS with a functionally equivalent label.

In regard to extinction coefficient or quantum yield, the art is replete with luminous labels and it is noted that Applicant has not pointed to the criticality of these variables. Therefore, the extinction coefficient or quantum yield in the labels used in the method are recognized results-effective variables and well within the purview of the skilled artisan in the absence of unexpected results.

The prior art references are silent in regard to configuration of measuring compartments and emergence objective. However, it is again noted that Applicant has not pointed to the criticality of these variables. Therefore, the configuration used in the method are recognized results-effective variables and well within the purview of the skilled artisan in the absence of unexpected results.

The prior art references are also silent in regard to use of a microdispensing system for dispensing the sample volumes. However, one of ordinary skill in the art would expect that microdispensing systems (which read on a pipetteman) would be used as the volumes are small. Alternatively, it would be obvious to one of ordinary skill in the art to dispense the sample volumes with a microdispensing system because the volumes are small.

The references are silent in regard to forcing sample through and/or trapped by a rectified or alternating electric field. However, such means of transporting or trapping ionic samples is well known, and functionally equivalent to means such as manually dispensing sample on a coverslip and trapping by physical means in that the end result, e.g. trapping sample to successfully complete fluorescent measurements. Alternatively, such means are considered well with in the purview of one of ordinary skill in the art in the absence of unexpected results.

It may be determined that the teachings of the prior art differ from the instant invention in that the reagents are not concentrated, either by increasing the effective association rate, and the teachings of the prior art differ from the instant invention in that the reagents are not concentrated by concentrating the reactants prior to mixing them via a technique such as electrophoresis and transporting the reagents to the measuring volume element via electrophoretic step(s).

However, it is well known that rate of chemical reactions and equilibrium concentrations of product are increased by concentration of the reacting components. All of the above cited references teach either the potential or utilization of FCS to examine equilibrium dynamics or molecular processes. It is also well known in the art that electrophoresis may be used for concentration and /or transport of reagents and that concentration of the reacting components can be effected by reducing the effective reaction volume by changing the hydration sheath around the reactants (e.g. by adding polymers or dextrans).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to concentrate the reagents by increasing the effective association rate of the reagents by one of the many methods known in the art (e.g. by adding polymers or dextrans) or by electrophoresis prior to mixing (reagents may be transported by electrophoresis in one or multiple steps as well) because molecular processes and equilibrium dynamics are effected by concentration of reagent and all of the above cited references teach either the potential or utilization of FCS to examine equilibrium dynamics or molecular processes. One of ordinary skill in the art would have been motivated to concentrate the reagents by increasing the effective association rate of the reagents by one of the many methods known in the art (e.g. by adding

polymers or dextrans) or by electrophoresis prior to mixing because of the expectation of successfully increasing the ability of FCS to measure equilibrium dynamics or molecular processes by increasing the probability that the intermolecular processes will occur in the small test volume.

The teachings of the prior art differ from the instant invention in that (a) two analytes are not measured each with a different dye label via energy transfer or through the differing wavelengths of excitation or emission of the labels (b) in particular using the method for measurement of lipid-bearing vesicles or proteins made by in vitro synthesis or polymer distributions (c) the biological materials are not arranged in two dimensional sheets or immobilized structure.

However, (a) energy transfer by two dyes is well known in the art to measure bimolecular or higher reaction parameters (such as distance between the reactants, etc) and all of the above cited references teach either the potential or utilization of FCS to examine equilibrium dynamics or molecular processes; (b) all of the above cited references teach that FCS may be generally applied to biological reactions and models, which will include measurement of lipid-bearing vesicles or proteins made by in vitro synthesis or polymer distributions (see in particular Meyer et al for lipid); (c) it is well known that many biological systems rely on strict spatial order between components for function, and in particular Thompson et al teach an application of FCS is to study specific binding characteristics between chemical species, one of which is immobilized upon a surface (e.g. page 104, right column) and that cell integrity is important in some applications (e.g. page 104, left column, study of motion of muscle crossbridges).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to (a) use two dyes to measure two reactants in a bimolecular reaction or higher, or (b) use the method of the cited references to study lipid-bearing vesicles or proteins made by in vitro synthesis or polymer distributions, or (c) immobilize the biological material on a "sheet" structure, because all of the above cited references teach either the potential or utilization of FCS to examine equilibrium dynamics or molecular processes (which can be bimolecular or higher) and (a) energy transfer by two dyes is well known in the art to measure bimolecular or higher reaction parameters (b) important biological systems amenable for FCS study including lipid-bearing vesicles or proteins made by in vitro synthesis or polymer are known, and (c) it is well known that many biological systems rely on strict spatial order between components for function and this order can be preserved by immobilizing biological structures on sheets. One of ordinary skill in the art would have been motivated to (a) use two dyes to measure two reactants in a biomolecular reaction or higher, or (b) use the method of the cited references to study lipid-bearing vesicles or proteins made by in vitro synthesis or polymer distributions, or (c) immobilize the biological material on a "sheet" structure, because of the expectation of successfully using FCS to examine important biological reactions.

Response to Arguments

12. Applicant's arguments filed 6/23/98 (Paper No. 20) have been fully considered but are not persuasive.

Applicant argues on page 8 regarding a similar 112(2) rejection for omission of methods steps that it is not necessary to recite each and every element needed for the practical utilization of claimed invention. This is not persuasive because, as above, the lack of correlation renders the claims vague and indefinite and thus the "legal limits of the invention" are not defined.

13. Applicant's arguments filed 6/23/98 (Paper No. 20) have been fully considered but are not persuasive.

For both anticipatory and obviousness type rejection, Applicant argues on page 9-11 that the measuring volume of less than or equal to 10^{-14} l is not taught. However, e.g. Rigler, on page 13 (Introduction"), teach that the measuring volume can be 10^{-15} l and below.

Conclusion

14. No claims are allowed.

15. A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

16. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current official FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Heather Bakalyar, whose telephone number is (703) 305-7143. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM. If attempts to

reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, Ph.D., can be reached at (703) 308-4310.

Heather A. Bakalyar, Ph.D.
Patent Examiner
9/13/98

PAULA K. HUTZELL
SUPERVISORY PATENT EXAMINER